Cleveland Clinic

Ethical Implications of Affordable Whole-Genome Sequencing

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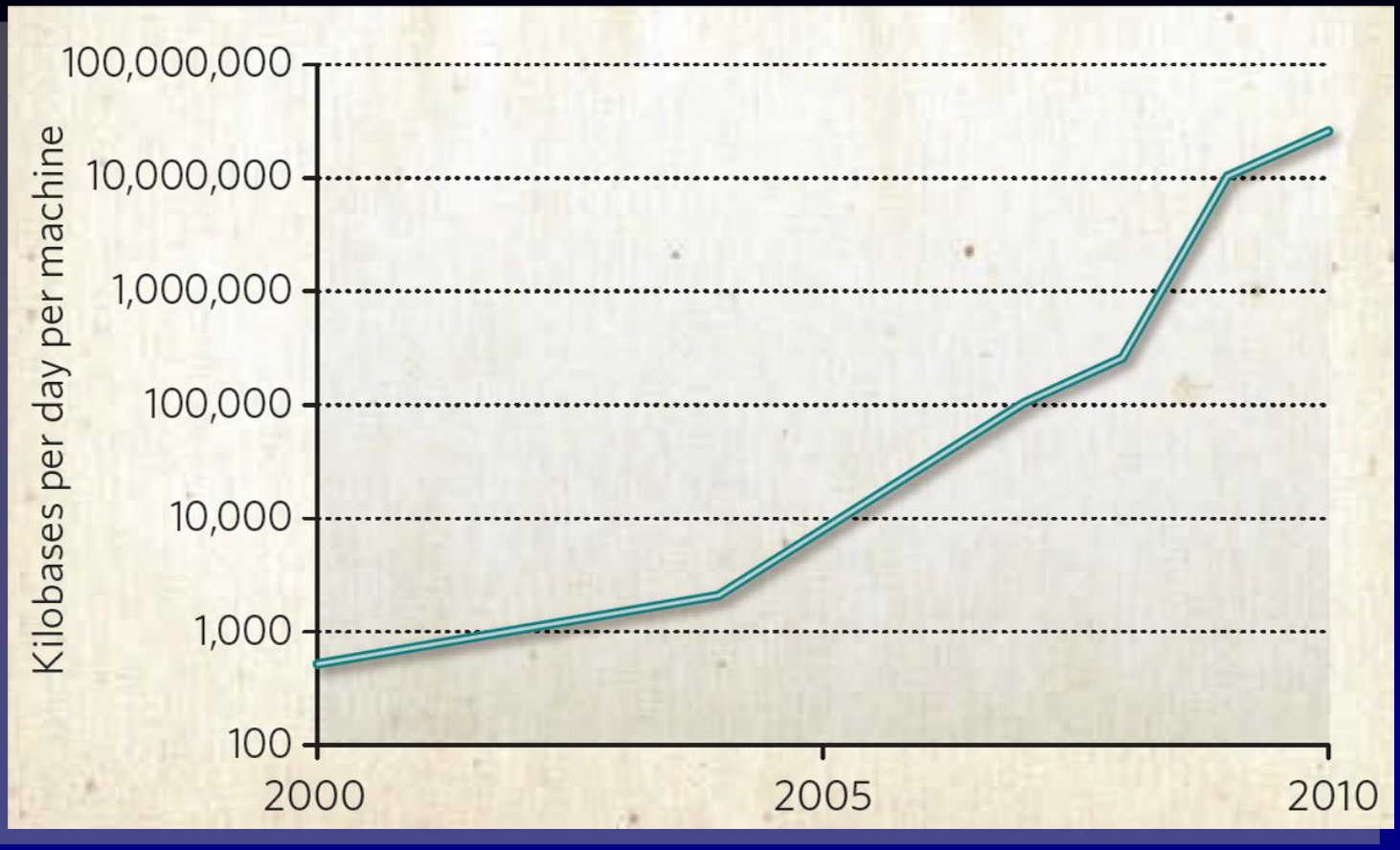
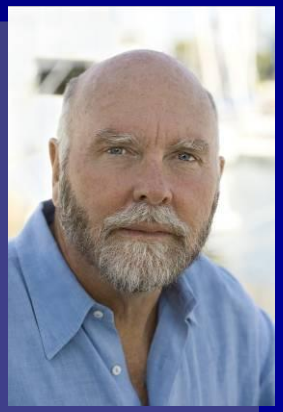
Disclosure

- Dr. Sharp has no financial relationships of any kind with any for-profit company involved in the development of genetic testing.
- Dr. Sharp is the Principal Investigator on two research grants from the National Institutes of Health examining patient perspectives on genomics and personalized medicine (R01 HG004500, R01 HG004877).





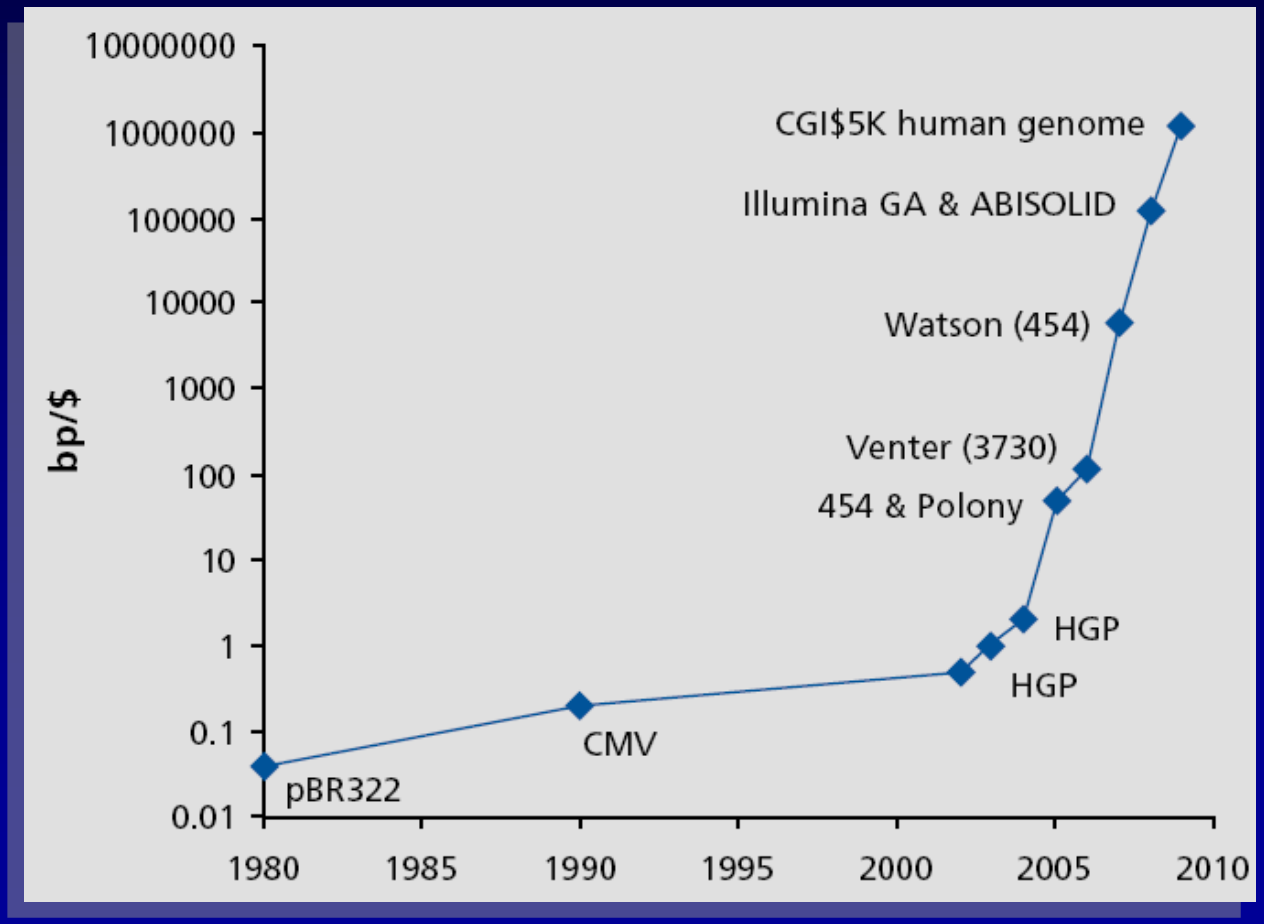
“Genomes can now be sequenced around 50,000 times faster than in 2000.”

J Craig Venter PhD

Nature 2010;464:676.

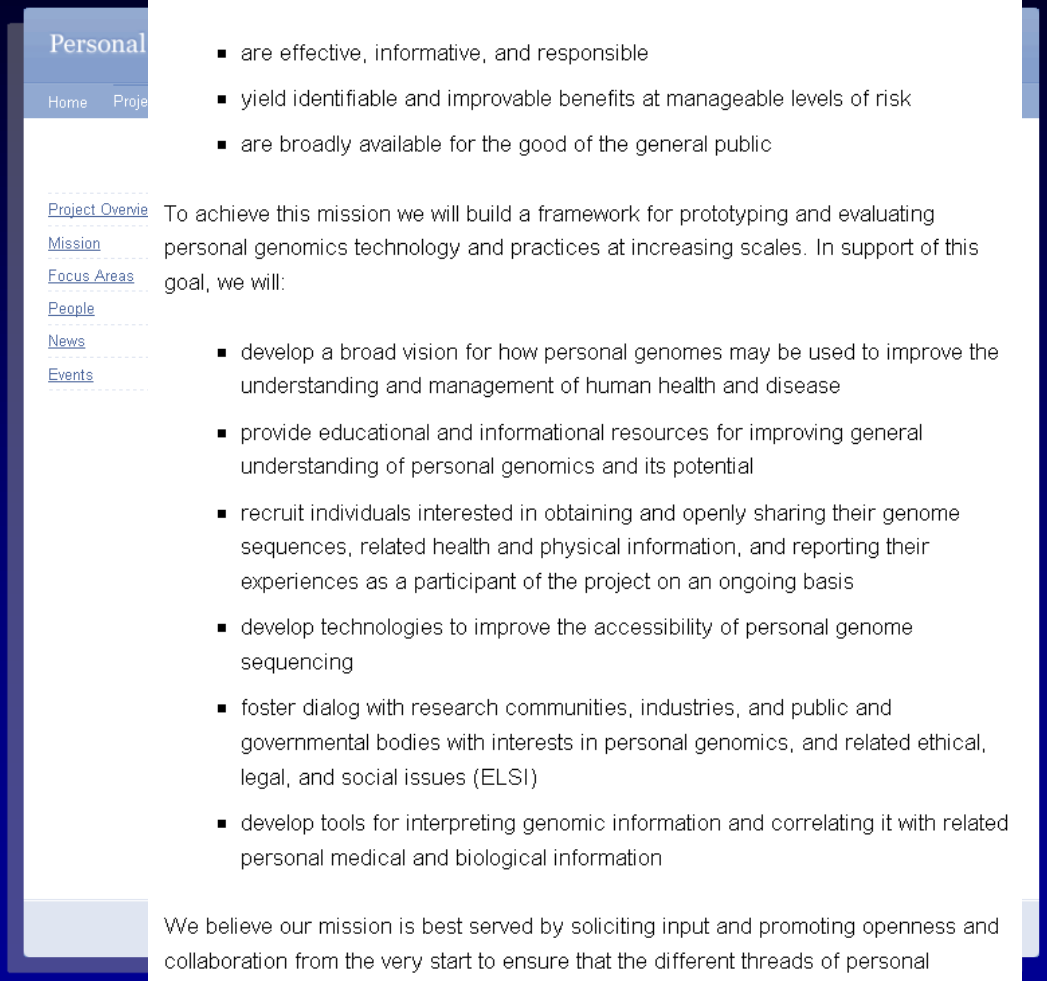
"[recent] developments suggest that technology capable of meeting the cost target of $1000 or less for a diploid human genome sequence is within reach."

Jeantine Lunshof PhD



Lunshof et al. Dialogues Clin Neurosci 2010;12(1).

Pers ect



Mission

The mission of the Personal Genome Project is to encourage the development of personal genomics technology and practices that:

- are effective, informative, and responsible
- yield identifiable and improvable benefits at manageable levels of risk
- are broadly available for the good of the general public

To achieve this mission we will build a framework for prototyping and evaluating personal genomics technology and practices at increasing scales. In support of this goal, we will:

- develop a broad vision for how personal genomes may be used to improve the understanding and management of human health and disease
- provide educational and informational resources for improving general understanding of personal genomics and its potential
- recruit individuals interested in obtaining and openly sharing their genome sequences, related health and physical information, and reporting their experiences as a participant of the project on an ongoing basis
- develop technologies to improve the accessibility of personal genome sequencing
- foster dialog with research communities, industries, and public and governmental bodies with interests in personal genomics, and related ethical, legal, and social issues (ELSI)
- develop tools for interpreting genomic information and correlating it with related personal medical and biological information

We believe our mission is best served by soliciting input and promoting openness and collaboration from the very start to ensure that the different threads of personal genomics are all individually addressed and reinforce each other as they come together. Toward this end, we seek the involvement of individuals from research communities, industry, public bodies, and other stakeholders interested in contributing to our mission. **Contact us**.

personalgenomes.org/mission.html

“Health professionals are now faced with the prospect of their patients coming to the office, DNA profile in hand, asking for preventive management tailored to their specific disease risks.”

Kenneth Offit MD MPh

JAMA 2008;299(11):1353.

Ethical and Social Challenges

- Are physicians ready?
- What results do we return? When? How?
- What are our fiduciary responsibilities? To whom?
- How do we manage the many ethical unknowns?

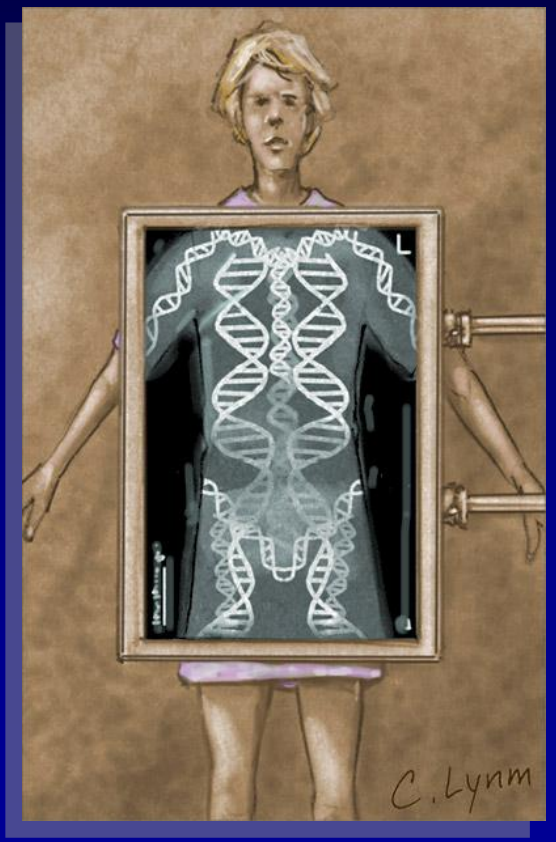


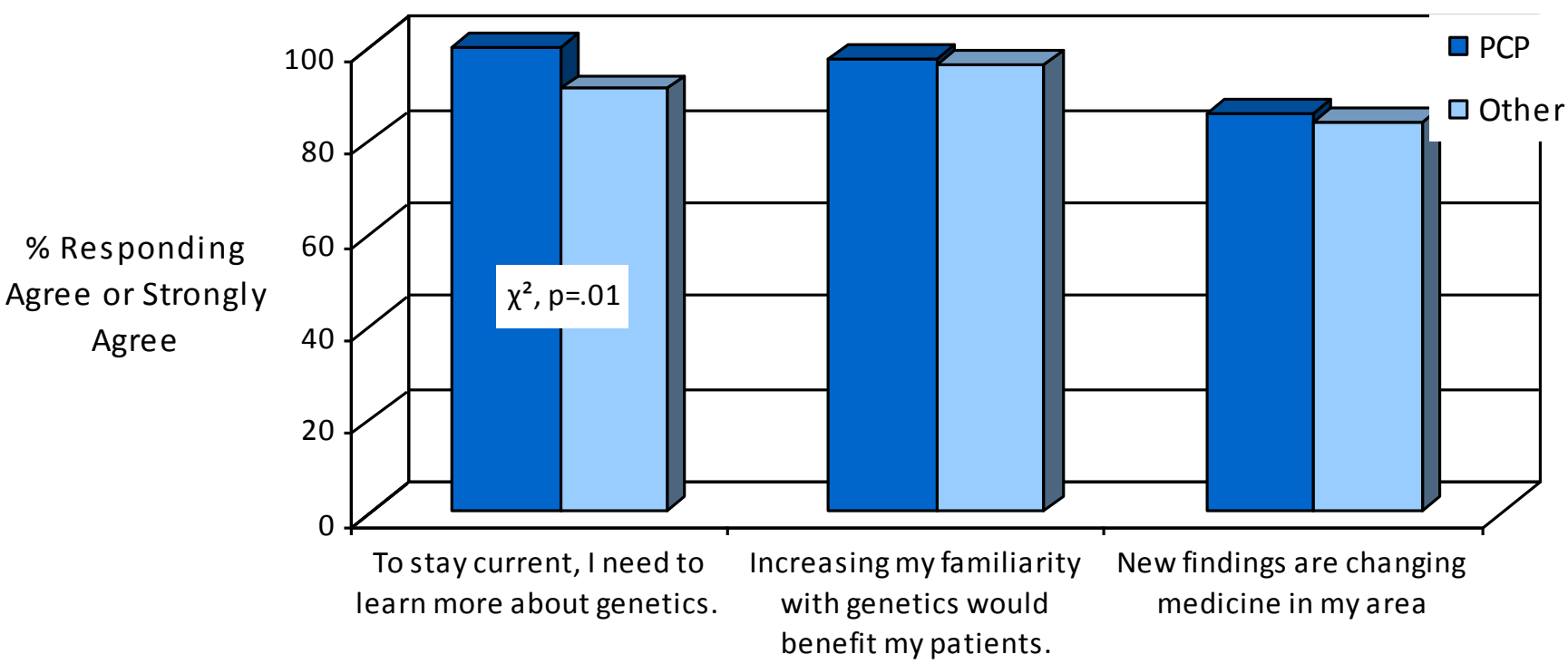
Table 1. Respondent characteristics (n=145)

Characteristic	*n*	*%*
Sex, female	46	31.9
Age, years (48, 11)*		
20-29	5	3.8
30-39	29	22.1
40-49	35	26.8
50-59	45	34.4
60-69	17	13.1
≥70	2	1.6
Medical education, U.S.	110	78.6
Primary specialty		
Internal medicine	57	41.6
Family medicine	15	10.9
Pathology or Radiology	14	10.2
Surgery	11	8.0
Obstetrics/gynecology	10	7.3
Anesthesiology	9	6.6
Pediatrics	7	5.1
Ophthalmology	6	4.4
Neurology	6	4.4
Other	2	1.5

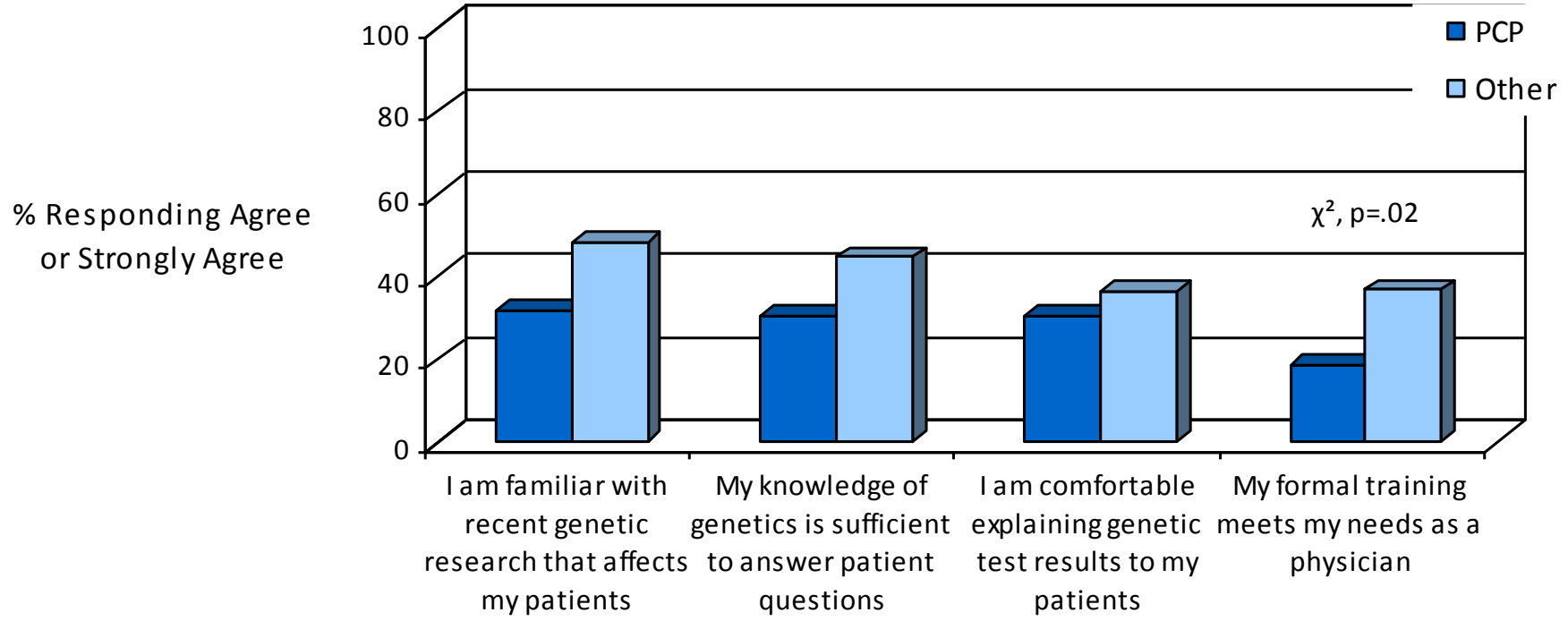
**mean, SD*

A Study of Physician Views of Genetics

Physicians Want More Education About Genetics



Familiarity with Clinical Genetics by Physician Specialty



Are Physicians Ready for WGS?

- Many physicians don't feel prepared to counsel patients about *currently available* genetic tests:
  - Very unlikely to be familiar with genomic analyses.
- Not a simple matter of improving physician knowledge:
  - Appeal of personalized medicine lies in its potential to transform medical practice itself.
  - Shift from episodic disease care to proactive health management.
- Many physicians may not be well prepared for that more fundamental shift signaled by affordable whole-genome sequencing.

Deciding Which Results to Return

- Whole-genome sequencing will reveal many types of genetic information that was not anticipated.
  - Many of these possibilities cannot be discussed in depth prior to testing, e.g. findings related to rare mutations.
- This limitation calls into question the possibility of informed patient consent.
- Need to develop new approaches to discussing the types of diagnostic possibilities associated with genomic testing.

Study Aims

- **Describe** patients' and genetic professionals' attitudes and beliefs about:
  - the types of diagnostic possibilities that should be discussed prior to large-scale clinical mutation testing.
  - the types of diagnostic results that should be returned after testing (respective priorities).

Goal: Develop practical guidance on the return of diagnostic results from genomic tests.

Approach

- In-depth qualitative data from:
  - Patient interviews
  - Expert advisory groups of genetics professionals
- Surveys of patients for whom personal genomic testing may be appropriate in the future.
- Expert advisory committee to consider the practical implications of our findings

Expert Advisory Groups

- Groups of 8-10 genetic professionals at six partner institutions
  - Expertise in clinical genetics, genetic counseling, public health genetics, bioethics, etc.
  - 6 regional sites: Ann Arbor, Baltimore, Cleveland, Denver, Philadelphia, Seattle
- Advisors attend a series of 4 two-hour meetings to discuss clinical aspects of highly multiplexed ("genomic") testing
  - Mock patients and diagnostic results reviewed and discussed
  - Focus on practical strategies for increasing pt understanding
- Round 3 meetings complete at all 6 sites (18 meetings)

Expert Advisory Groups

Major findings (preliminary):

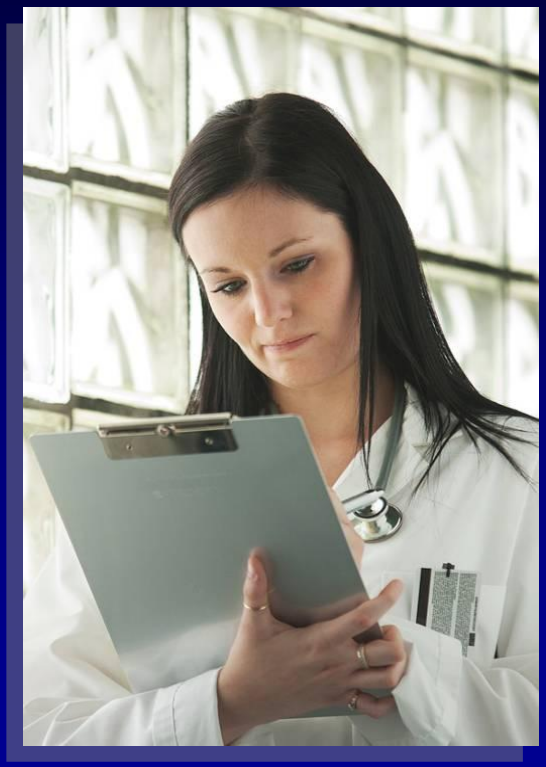
- **Genetics professionals do not believe that highly multiplexed genetic tests are ready for routine clinical use**
- Many geneticists feel that there is insufficient data to support the clinical utility of multiplexed genetic testing;
- It will be difficult to place patients in a position to provide informed consent to multiplexed genetic analyses; and
- Widespread use of multiplexed genetic tests may result in unnecessary medical follow up of false test results and other findings that are not immediately relevant to the patient's clinical presentation (e.g., risks for later onset diseases, recessive mutations relevant to reproductive decisions, etc.)

Prioritizing Results

- Genetic professionals struggled to say which kinds of test results should be "high priorities" to review with patients.
- Once results are generated, they felt that *all medically relevant information* should be reviewed.
- Many clinical geneticists favored a more targeted approach to disease diagnosis, in which a clinician orders only those tests that are suggested by a patient's presentation/history.
- Since whole-genome sequencing will reveal many types of genetic information that are not immediately relevant to patient care/diagnosis, they saw WGS as raising multiple problems of information management.

  - These are the medical professionals with the most extensive experience with genetic testing and they are urging caution with regard to clinical applications of WGS.

How to Manage WGS Data



- Once we create WGS data, several additional issues will need to be resolved re the management of that data:
  - Duty to warn
  - Need to recontact
  - Patient requests for findings of personal interest

“Duties to Warn”

Suppose you learn that someone in your patient’s family is at increased risk of disease.

Are you required to notify that person?

- **Legal requirements are unclear**
- **Professional expectations are better defined**

When Should Others Be Warned?

Legal cases

- ***Pate v. Threlkel,*** 1995; Florida, hereditary thyroid cancer
  - Physician must inform the patient of possible implications for others
- ***Safer v. Estate of Pack,*** 1996; New Jersey, colon cancer
  - Physician must take "reasonable steps" to warn other immediate family members at risk [direct notification of persons at risk?]

Professional guidance

- **ASHG 1998:** risk-benefit assessment of need for disclosure
- **ASCO 2003:** discuss with the patient the need to inform others
- **AMA 2004:** offer to assist in communicating risks to others

Revisiting WGS Data

- Reinterpretations of WGS data will continue indefinitely:
  - When should a patient be recontacted about new findings?
  - How vigilant should physicians be in reviewing WGS data to determine if any new findings may be relevant to the proband?
- Should patients be given their personal WGS data and allowed to interrogate that data as they'd like?
  - Restricting access seems inappropriately paternalistic (and may not be legal)
  - Restricting access also seems to encourage genetic exceptionalism
  - Not restricting access may distribute WGS data in ways that are socially problematic (patient enabled web-based dissemination)
  - No good data management approach available
  - Many common misunderstandings of genetic information

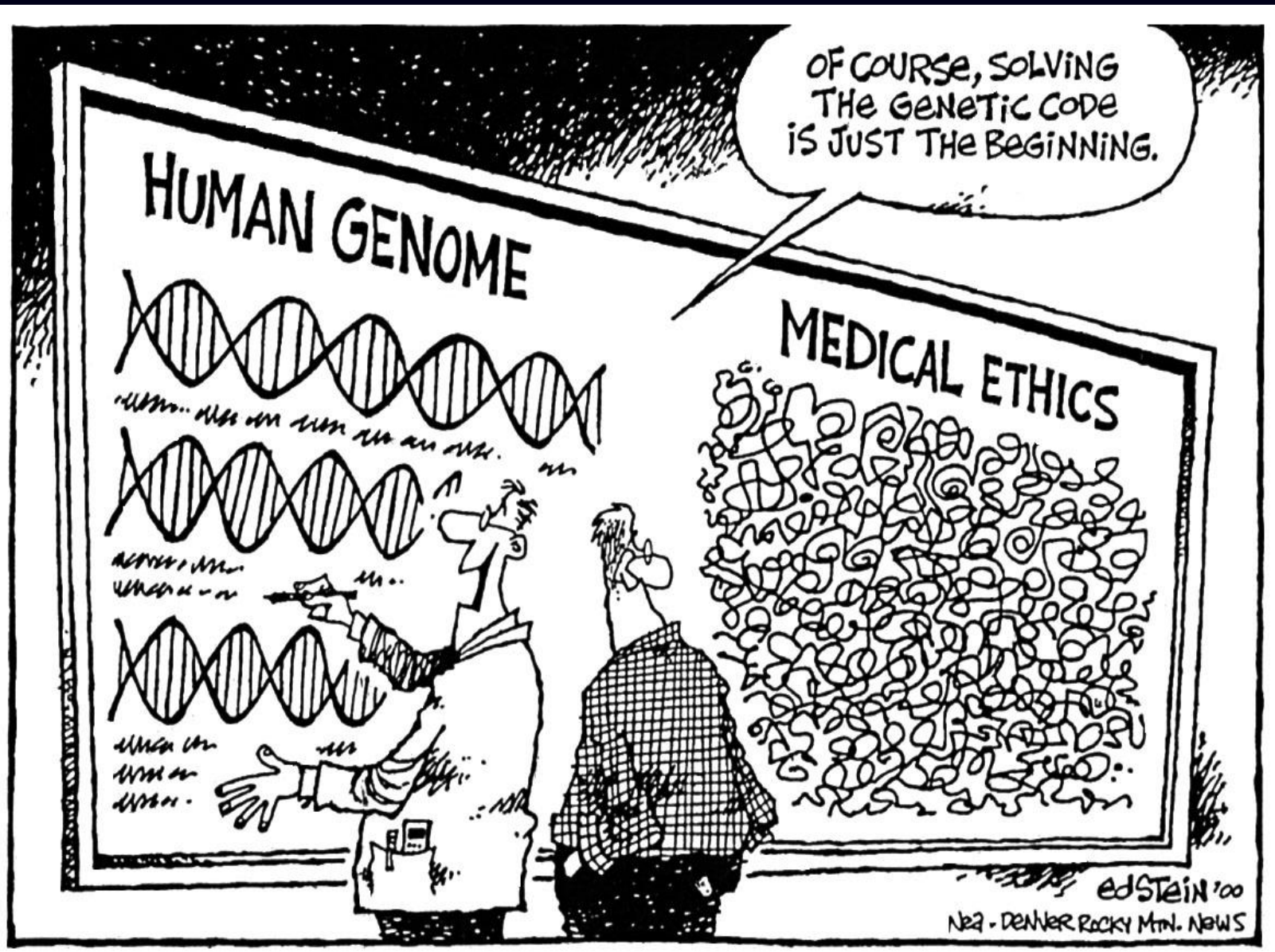
Views of Genetics

Too Many Unknowns

Need for research on ethical, legal, & social dimensions of genomic medicine.

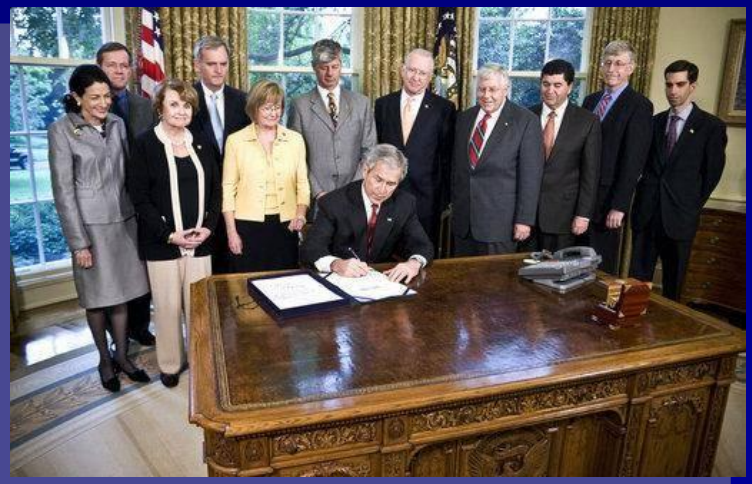
Research Needs

- Is personal awareness of genetic risk factors predictive of improved health outcomes?
- Which models of information delivery enhance pt understanding of risk factors (gx and non-gx)?
- How can we equip physicians with the tools they need to deliver predictive information efficiently and more effectively?
- What patient burdens and non-financial costs may be associated with earlier identification of disease (anxiety, distress, moral judgments)?
- How can we do a better job of motivating patients to engage in activities that promote good health? [Smoking, diet, exercise, etc.]
- How can we encourage physicians and other healthcare professionals to discuss inherited risks, disease prevention, etc.?
- What are the broader societal implications of personalized medicine and whole-genome sequencing?


OF COURSE, SOLVING THE GENETIC CODE IS JUST THE BEGINNING.
HUMAN GENOME
MEDICAL ETHICS
edSTEIN '00
NEA - DENVER ROCKY MTN. NEWS

GINA

- Genetic Information Nondiscrimination Act
  - H.R.493 signed into law May 21st, 2008
- Covers
  - Employment (November 2009)
  - Health Insurance (May 2009)
- Does not cover
  - Long-term Care Insurance
  - Disability Insurance
  - Life Insurance
  - Military



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Every life deserves world class care.